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Paraquat Poisoning—Lung Transplantation

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[WITH SPECIAL PLATE]

Brit. med. J., 1968, 3, 759-763

Summary: A 15-year-old boy ingested a mouthful of paraquat and developed severe respiratory distress. Treatment included the transplantation of one lung, but subsequently changes developed in the graft which are thought to have been due to paraquat, and the patient died two weeks after the operation.

The dangers of keeping poisonous substances in incorrectly labelled bottles has once again been demonstrated, while the pattern of paraquat poisoning, especially the development of proliferative alveolitis and terminal bronchiolitis, is confirmed.

Immediate forced diuresis followed by haemodialysis is necessary to remove paraquat, thereby perhaps avoiding initiation of the changes in the lungs. The technical feasibility of human lung transplantation has again been demonstrated. It has also been shown that infection does not necessarily pose an insuperable problem, at any rate if, as in the case described, there was no preoperative pulmonary infection in either recipient or donor.

Introduction

Fatal poisoning by the weedkiller paraquat (1,1'dimethyl-4,4'-dipyridilium, Gramoxone W) has previously been recorded in adults (Bullivant, 1966; Almog and Tal, 1967; Oreopoulos *et al.*, 1968) and in children (*Brit. med. J.*, 1967; Campbell, 1968). We report the findings in a youth of 15 who showed the expected features of hepatic, renal, and pulmonary toxicity. The deterioration in respiratory function was treated by lung transplantation.

Case Report

The Scottish Poisons Information Bureau received a telephone call at 01.15 hours on 9 May 1968 from Lewis Hospital, Stornoway, requesting information regarding the possible toxic effects of the herbicide Gramoxone W (paraquat). On the previous day the weedkiller in the undiluted form from a bottle labelled Kola had been ingested accidentally by a 15-year-old boy. The amount swallowed was at the most one mouthful. The inquirer was informed of the grave effects which could arise and emergency measures were outlined. The patient was treated by a forced osmotic diuresis and passed 4.7 litres of urine over the next 14 hours. Later that day the further management was discussed with the consultant in charge of the patient. It was advocated that during the latent period, when

the effects of the poison would be limited to the upper alimentary tract, the patient be flown to a centre where the expected severe respiratory, renal, hepatic, and biochemical difficulties could be more readily dealt with. The consultant elected to send the patient to the Regional Poisoning Treatment Centre, Royal Infirmary, Edinburgh, where he arrived by air ambulance on 10 May.

The patient was slim, weighing 52 kg. (115 lb.). There were very painful burns of the tongue, mouth, and fauces, but no other abnormal clinical features. He had no previous significant history and he was a well-balanced, intelligent, and stoic individual. Large amounts of paraquat were present in the urine passed within 12 hours of ingestion. The chest radiograph, haemoglobin, white cell count (total and differential), and E.S.R. were normal, but the urine contained a trace of albumin and the blood urea was 82 mg./100 ml. The alkaline phosphatase was 40 K.A. units/100 ml., the bilirubin 0.8 mg./100 ml., and the serum alanine aminotransferase 34 units/ml.

Symptomatic treatment of the mouth, a second forced diuresis, prednisone 200 mg. daily, and penicillin were given.

In the expectation that a relentless proliferative alveolitis and terminal bronchiolitis would soon develop, an opinion regarding lung transplantation was sought. It was agreed that lung transplantation should be undertaken if deterioration in pulmonary function was demonstrated.

Respiratory function tests were undertaken by Dr. G. J. R. McHardy on 11 May, when clinically and radiologically the patient was well. They showed moderate reduction in ventilatory capacity of an obstructive pattern (see Table). When repeated two days later there was further deterioration, though clinically the patient was reasonably well despite the local lesions, mild jaundice, and a raised blood urea. It was therefore decided that lung transplantation should be undertaken and various units were alerted for potential donors.

Respiratory Function Tests

At Rest, Breathing Air	Predicted for Age 15 and 165 cm. Height	11 May	13 May
T.L.C. (l.)	4.7	—	2.77
V.C. (l.)	3.6	—	1.22
R.V. (l.)	1.0	—	1.54
R.V./T.L.C. (%)	21	—	55
F.E.V. ₁ (l.)	> 3.3	1.1	0.72
F.V.C. (l.)	3.6	2.05	1.1
F.E.V./F.V.C. (%)	91	53	65
Pao ₂ (mm. Hg)	—	86	80
PaCO ₂ (mm. Hg)	—	37	34
pH	7.45	25	20
Derived bicarbonate	—	16	27
PA-aO ₂	About 12	15	7
Tco (single breath)	> 30	—	—

On 15 May, six days after ingestion, there was clear evidence that the lungs were severely involved, as there was now respiratory distress and x-ray examination showed a fine granular change in the midzone of the left lung. That evening an 18-year-old girl who two days previously had ingested a large amount of paracetamol and ferrous sulphate died from gastrointestinal haemorrhage. The

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acute massive necrosis of the liver induced by these drugs (Luongo and Bjornson, 1954; Davidson and Eastham, 1966) had so prolonged the prothrombin time that the severe haemorrhage from the alimentary tract could not be stemmed. Her lungs were thus available for transplantation.

Operation

As soon as the donor was pronounced dead artificial ventilation was continued. Mr. J. D. Wade performed left thoracotomy. The pericardium was opened from diaphragm to aortic arch. There was a large haemopericardium. The left atrium was drained and the left lung was perfused with Koff's solution (Dunea *et al.*, 1965) at 4° C. through a needle in the main pulmonary artery. After 20 minutes of this perfusion the effluent was clear and colourless. The lung was removed with long segments of its main bronchus and pulmonary artery and a ring of atrium continuous with the left pulmonary veins. White froth exuded from the bronchus. There were no superficial pulmonary haemorrhages. The resected lung was covered with a cold moist pack and transferred to the recipient operating-theatre.

Simultaneous with this procedure a left thoracotomy through the bed of the sixth rib was performed on the recipient under general anaesthesia induced with thiopentone sodium 125 mg., curare 45 mg., and maintained with nitrous oxide and oxygen. As soon as the pleura was opened the lung shrank away and became atelectatic, showing no response to positive-pressure ventilation by the anaesthetist. Its surface was reddish-plum-coloured and flecks of fibrin lay on it. There was a pleural effusion of about 200 ml. of clear straw-coloured liquid. None of the visible lymph nodes was pathologically enlarged. The lung was resected. The hilar pleura and fascia were divided on the pulmonary parenchyma and reflected towards the mediastinum so that a viable cover for the hilar structures was preserved. The left pulmonary artery was divided at the level of its first segmental branch. The main bronchus was divided just proximal to its upper branch. The bronchial vessels were divided at a point peripheral to the level of bronchial section and preserved undamaged up to that point. There was no excess of mucus in the bronchus. The pericardium was opened and the veins were divided at their junction with the left atrium.

The donor lung was now trimmed. The hilar pleura and subpleural fascia were reduced to a narrow rim close to pulmonary parenchyma. All atrial muscle was removed from the conjoined pulmonary veins. The bronchus was divided just proximal to the origins of the upper and apical lower bronchi. The pulmonary artery was divided, leaving a 1-cm. length proximal to its first segmental branch. During manipulation froth poured from the bronchus and continued to do so as long as the bronchus remained open. The donor lung was sutured in position. First the veno-atrial anastomosis was made with an anterior and a posterior continuous suture of 0000 silk. When this anastomosis was complete the atrial clamp was removed so that blood came freely back through the donor pulmonary artery, displacing air and Koff's solution. This was done with the intention of avoiding air embolism but with some doubt about its advisability, since the recipient was not heparinized and there might be risk of pulmonary vascular obstruction by thrombosis. The pulmonary arteries were anastomosed with a similar suture and the circulation through the lung was established. The bronchi were anastomosed with simple interrupted sutures of 00 silk.

The hilar sheath of the recipient was sutured with 0000 silk interrupted sutures to the cuff of pleura at the edge of the donor parenchyma. Pericardium and aortic sheath of the recipient were used to strengthen this hilar cover in front of and behind the bronchial suture line. At this stage the transplanted lung looked and behaved in response to manipulation by the anaesthetist like a normal lung.

A low intercostal drain was introduced. The chest wall was closed with silk sutures. Suction at 5 mm. mercury negative pressure was applied to the drain.

Pathology of Resected Lung

The pleural surface of the left lung removed at operation showed scattered small foci of congested blood vessels sometimes covered by a thin layer of fibrin and also small underlying intrapulmonary

haemorrhages. The cut surface showed further small haemorrhages deep in the lung here and there, and with the dissecting microscope slight thickening of the alveolar walls could be seen in some places.

Histologically, the thickening was due to infiltration by neutrophils, lymphocytes, macrophages, and fibroblasts (Special Plate, Fig. 1). Within the lumen of the first order of respiratory bronchioles there were commonly some large alveolar cells with abundant cytoplasm. No hyaline membranes were seen. The appearances were considered to be compatible with the effects of paraquat ingested seven days previously.

Postoperative Progress

The operation was complete two and a half hours after the death of the donor. The recipient made a normal immediate recovery from thoracotomy. A radiograph on the first postoperative day showed the left lung completely expanded but with residual changes of pulmonary oedema. The intercostal drain was removed. Because the painful ulcers in the mouth made it difficult to give him enough liquid, intravenous infusion of dextrose was continued. Most of the time he wore a mask giving air enriched with oxygen to approximately 30%. He expectorated small quantities of clear serous liquid. Penicillin 6 mega units daily was given, and at no time were organisms insensitive to penicillin found in the sputum. Daily radiographs of the chest showed a gradual diminution of the opacity on the left. Three days after operation crepitations were heard over the lower part of the right lung and the chest x-ray film two days later showed mottled opacities on that side.

Apart from the changes in the right lung which progressed, the effects of paraquat on the patient's own other organs steadily improved. Urinary output was adequate and the blood urea, serum bilirubin, and analine aminotransferase, respectively 160 mg./100 ml., 5.5 mg./100 ml., and 830 units/ml. at operation, fell to 65 mg./100 ml., 2.6 mg./100 ml., and 61 units/ml. respectively at death. The alkaline phosphatase had fallen from 50 to 17 K.A. units/100 ml. at death.

The initial electrocardiograms showed prominent U waves, but no abnormality was demonstrated except in the immediate post-operative phase, when changes of pericarditis were understandably evident.

On 22 May there was a minute pneumothorax on the left side, and the possibility of leakage at the bronchial anastomosis was considered. The air had been absorbed by the following day, but the opacities in the right lung had increased in density and extent, and similar changes were evident in the left lung. The respiratory rate rose to 30 per minute. By 25 May he was obviously ill. There was again a small pneumothorax, and on 26 May the haemoglobin was 68% and 2 pints (1,140 ml.) of fresh genotyped blood was transfused. The following day he was in severe respiratory difficulty, which was not appreciably diminished by intubation of the pneumothorax and pulmonary re-expansion. An endotracheal tube was passed for assisted ventilation, but despite this he remained cyanosed. Respiratory deterioration continued until he died on the evening of 28 May.

Immunosuppression

Prednisone, which had been started four days before operation, was continued thereafter in a dosage of 200 mg. daily until the sixth postoperative day, after which the dose was reduced by 10 mg. daily. Hydrocortisone 100 mg. was given intravenously during the operation. The patient was given mercaptopurine intramuscularly and thereafter azathioprine by mouth in the dosage shown in Fig. I. Aluminium hydroxide was given three-hourly (omitting one dose during the night) to reduce the risk of steroid-induced peptic ulceration.

In view of the lack of known criteria for recognizing rejection of a lung transplant our aim was to push the level of immunosuppression near to but not beyond the limit of safety, taking into consideration the patient's weight, general condition, and initial period of impaired renal function. In retrospect, the dosage seems to have been right, since there were no serious complications attributable to the immunosuppression and no post-mortem evidence of transplant rejection.

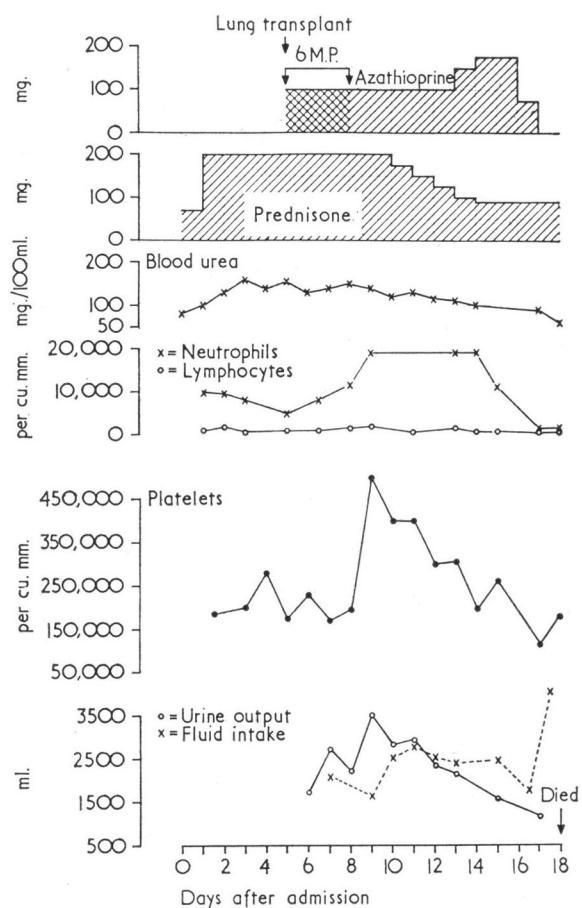


FIG. I

Toxicological Analyses

The detection and estimation of paraquat was undertaken by Dr. S. L. Tompsett and Dr. S. S. Brown of the subunit for toxicology of the University Department of Clinical Chemistry, Royal Infirmary. The method was based on the colour reaction described by Calderbank and Yuen (1965) but possessed the advantage that it may be carried out much more quickly, and even in the ward side-room.

To 5 ml. of approximately neutral fluid are added approximately 0.1 g. of sodium hydrogen carbonate followed by approximately 0.1 g. of sodium dithionite (hydrosulphite). A blue colour develops almost immediately.

For quantitative purposes, measurements are made at 625 millimicrons. With the Unicam SP 600, paraquat in a concentration of 20 µg./ml. produces an absorbance approximating 0.72.

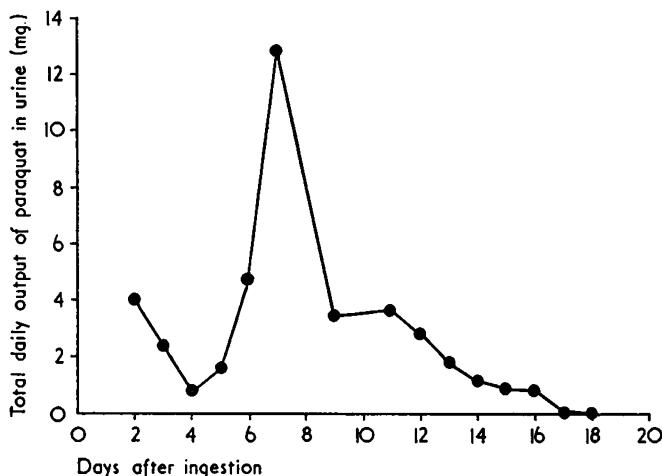


FIG. II.—Total daily amounts of paraquat recovered in urine.

In analysis of gastric contents and urine passed shortly after ingestion considerable dilution of the sample with water may be necessary. Detection and quantification of the small amounts likely to be encountered in the urine during the second and following days after ingestion may prove difficult. The procedure using a cation exchange resin described by Tompsett *et al.* (1961) and Tompsett (1968) has proved effective in these circumstances.

Results.—The specimen of urine passed 14 hours after ingestion contained 99 mg. of paraquat. The forced diuresis undertaken at Lewis Hospital, Stornoway, recovered 102 mg. of paraquat, while that after admission to this unit recovered 3 mg. The subsequent total daily amounts of paraquat recovered in the urine are shown in Fig. II. The lung removed at operation contained 850 µg. of paraquat per 100 g. of wet lung. Neither lung at necropsy contained any paraquat, nor was paraquat detected in the kidneys, liver, spleen, bone, or brain.

Post-mortem Findings

The post-mortem examination was begun 70 minutes after death. Small ulcers were present on the inside of the lower lip and on the tongue. The conjunctivae were moderately icteric but the skin was not affected.

The left pleural sac contained air and 200 ml. of straw-coloured fluid with some flecks of fibrin. The visceral pleura, especially that of the lower lobe, was covered with a thick layer of fibrin (Special Plate, Fig. 2). The right pleural sac contained 100 ml. of clear straw-coloured fluid and no fibrin or air. There were no fibrous adhesions in either pleural sac. The pericardium contained 10 ml. of clear straw-coloured fluid and communicated with the left pleural sac near the hilum. The heart was covered by a very thin layer of fibrin causing a dullness of the surface.

The lungs were immersed in water and redistended with air through the trachea; no air bubbles appeared from the specimen to indicate the origin of the left pneumothorax. Ten per cent. formal saline was run into the trachea and pulmonary trunk and the pressure maintained at 25–30 cm. for 72 hours (pressure-fixation). The external appearance of both lungs was similar, showing shrinkage and fine nodularity (Special Plate, Fig. 2). The cut surface of the right lung showed fibrosis and very fine emphysematous changes in all areas, especially severe at the bases (Special Plate, Figs. 3, 4, and 5). These areas also sometimes showed extensive haemorrhage. The bronchi contained a large quantity of pale yellow granular material, but the vessels were normal on dissection.

Histologically, fibrosis and haemorrhages were confirmed, and in addition there was hyaline membrane formation (Special Plate, Fig. 14). Many of the respiratory bronchioles and alveolar ducts were dilated and showed loss of alveolar walls (Special Plate, Figs. 4, 5, and 14). The epithelium of occasional bronchioles showed proliferation into alveoli (Special Plate, Fig. 9). Plump fibroblasts were a feature of some fibrous areas (Special Plate, Fig. 15). All changes observed were consistent with the effects of paraquat ingested three weeks previously.

The transplanted left lung was similar externally to the right with shrinkage and fine nodularity, but there was a prominent layer of fibrin over the surface (Special Plate, Fig. 2). The cut surface revealed more extensive fibrosis and shrinkage than on the right, so that more of the slice was paler and solid-looking. Alveoli were present near the apex (Special Plate, Fig. 11), and their outlines could be seen in some other areas, but they were often absent in regions of emphysema and fibrosis (Special Plate, Fig. 12). Dissection revealed intact anastomoses, and all vessels were patent with minimal thrombosis at the suture lines (Special Plate, Fig. 13). Histologically many of the changes in the transplant were similar to those in the right lung, with severe fibrosis due to plump proliferating fibroblasts (Special Plate, Fig. 8), and emphysema with dilated respiratory bronchioles and alveolar ducts and loss of alveolar walls (Special Plate, Fig. 6). There was also proliferation of bronchiolar epithelium into alveoli (Special Plate, Fig. 10). In addition, however, there was proliferation of large lining cells in some surviving alveoli (Special Plate, Fig. 16). There was no arteritis (Special Plate, Fig. 8), necrosis, or pneumonia. All blood vessels appeared patent and normal. The bronchial mucosa distal to the suture line showed superficial ulceration with fibrin and neutrophils replacing epithelium. At the suture line the proximal epithelium was regenerating. The bronchi contained inflammatory exudate.

Pathological changes in other organs were as follows: The heart (280 g.) was covered by fibrin, and there was slight thickening of the ventricular walls (left 17 mm., right 5 mm.). Histologically, the muscle fibres were moderately hypertrophied and there was organizing fibrin on the surface. A small ulcer was present at the upper end of the oesophagus. The stomach and intestines were normal. The liver (1,265 g.) was moderately bile-stained and histologically showed no necrosis, but there were some bile thrombi in the central zone. The pancreas and endocrines were normal. The spleen (65 g.) was soft. The bone marrow appeared normal macroscopically in the vertebrae, the sternum, and right femur. Histologically, however, the spleen, marrow, and lymph nodes showed depletion of lymphocytes and plasma cells, and absence of germinal centres due to the immunosuppressive therapy. The kidneys (150 g. each) were grossly normal, but histologically showed many casts in distal convoluted tubules. The ureters and bladder were normal. The testes showed a maturation arrest. The brain (1,570 g.) was congested and showed no lesions grossly or microscopically.

It was concluded from the pathological investigation of the lungs that the left lung had been transplanted successfully, and that there was no change which could be attributed either to rejection or to the operation. However, the transplant had undergone severe fibrosis and epithelial proliferation like the right lung, and it was considered that the most likely cause was the paraquat which was shown to be in the blood at the time of the operation.

Discussion

The toxicity of paraquat in laboratory animals has been described by Clark *et al.* (1966). They demonstrated that individual animals of the same species differed widely in their response to paraquat, and that dosing of fasting animals produced more severe effects. Clark *et al.* (1966) did not consider the characteristic pulmonary lesions were due to the cumulative effects of paraquat but attributed them to irreversible changes in the lungs induced by the substance following initial administration. These changes often appeared histologically some days after ingestion, but once they were evident clinically death occurred in a matter of a day or two. Barnes (1968) described paraquat as a "hit-and-run poison," since its effects became manifest long after it had left the injured tissue. He likened these poisons to single-dose chemical carcinogens such as dimethylnitrosamine.

The mechanism whereby the proliferative alveolitis and terminal bronchiolitis is brought about remains unknown. Paraquat is not volatile, and so far as is known is not excreted by the lungs. Nor is it necessary to postulate inhalation of the fluid during swallowing or vomiting, as the characteristic lung pathology has been observed in man after subcutaneous injection of approximately 1 ml. of a 20% solution of Gramoxone (Almog and Tal, 1967).

The minimal lethal dose of paraquat in man is not known. Death following ingestion of one mouthful has been reported (Bullivant, 1966; Oreopoulos *et al.*, 1968). Dr. J. C. R. Greig (personal communication) had under his care an 11-year-old boy in Lewis Hospital, Stornoway, at the same time as we were dealing with our patient. This boy had taken a mouthful of paraquat concentrate immediately after a large meal; vomiting was at once induced and thereafter he felt well. On admission to hospital for observation five days later, apart from ulceration of the tongue and fauces, there was no abnormality. The urine contained a trace of paraquat and continued to do so for eight days after ingestion, but the boy made an uneventful recovery. McKean (1968) reported survival after ingestion of a "mouthful of fluid from a soft-drink bottle which contained a solution of the weedkiller paraquat." The concentration of paraquat in the solution is not, however, stated.

The pattern followed by our patient strikingly resembles that described in animals by Clark *et al.* (1966). The youth took the paraquat on an empty stomach and unfortunately did not vomit for at least five hours, thus despite slow absorption a

considerable amount was taken up. Though repeated forced diuresis as suggested by Kerr *et al.* (1968) was undertaken, the toxic effects later became evident in the liver, kidneys, and especially the lungs. The damaged liver and kidneys steadily improved, and at no time was any neurological change evident. The damage to the lungs, however, pursued the expected relentless course. Respiratory function tests were abnormal, and deteriorated further before clinical or radiological signs became evident.

It was considered at the time and subsequent events have confirmed that lung transplantation offered the only possible hope of saving this patient's life. The four previously reported cases of human lung transplantation (Hardy *et al.*, 1963; Magovern and Yates, 1964; White *et al.*, 1966; Shinoh *et al.*, 1966) survived only 18, 8, 7, and 18 days respectively, but the absence of preoperative pulmonary infection in our patient, and a considerable experience of immunosuppression in renal transplant recipients, encouraged us to proceed.

Technically the transplant operation presented no major problem, and the operation was completed in two and a half hours. The immediate postoperative phase was uneventful, as was the progress for the ensuing week. The only difficulty was encountered from his painful mouth and throat, which made it impossible for him to take other than semifluid foods. The pneumothorax occurring on the seventh postoperative day raised some anxiety, as it seemed possible that the bronchial anastomosis might have broken down owing to the lack of a bronchial arterial circulation. These fears were, however, unfounded, as the pneumothorax was absorbed or, some of it being mediastinal, the air escaped into the neck.

The appearance of a reticular pattern in the right lung, first evident radiologically on 20 May, was to be expected, and function probably steadily and rapidly lessened in that lung.

It seemed, therefore, that respiration was being maintained mainly if not entirely by the transplant, though we were not able to confirm this by differential pulmonary function studies with xenon, as the necessary equipment was not available at the time.

Eight days after operation the chest film showed for the first time a reticular pattern in the transplanted lung. It seemed that this might be due to rejection or infection, or alternatively to paraquat poisoning affecting the transplant.

The consistently negative results of bacteriological culture of the sputum made infection appear unlikely. Rejection could not be ruled out but was thought unlikely in view of the fact that this rarely occurs so soon after kidney transplantation in patients receiving similar doses of azathioprine and prednisone, and it was therefore decided not to increase the already high dosage of these agents.

There remained the possibility of the changes being due to paraquat. Against this was the fact that Daniel and Gage (1966), using ¹⁴C-labelled material, had found that in rats paraquat was poorly absorbed and 90% was excreted in 24 hours. In these experiments, however, the dose did not exceed the LD₅₀ value for rats, and no animals showed toxic changes. In our patient, probably because of renal damage, the blood paraquat at the time of operation, seven days after ingestion, was 40 µg./100 ml. There seems little doubt that this amount was sufficient to initiate the changes in the donated lung. There is, however, no knowledge of the level of paraquat in the blood which will start the typical changes in man. On this account it is advocated that, following ingestion of paraquat concentrate in even the smallest amount, forced osmotic diuresis should immediately be undertaken while arrangements are being made for haemodialysis. Haemodialysis should be continued until the blood is clear of paraquat.

With the appearance of clinical and radiological changes in the transplanted lung, deterioration was rapid; the further pneumothorax was adequately dealt with, but the expanded

HENRY MATTHEW ET AL.: PARAQUAT POISONING—LUNG TRANSPLANTATION

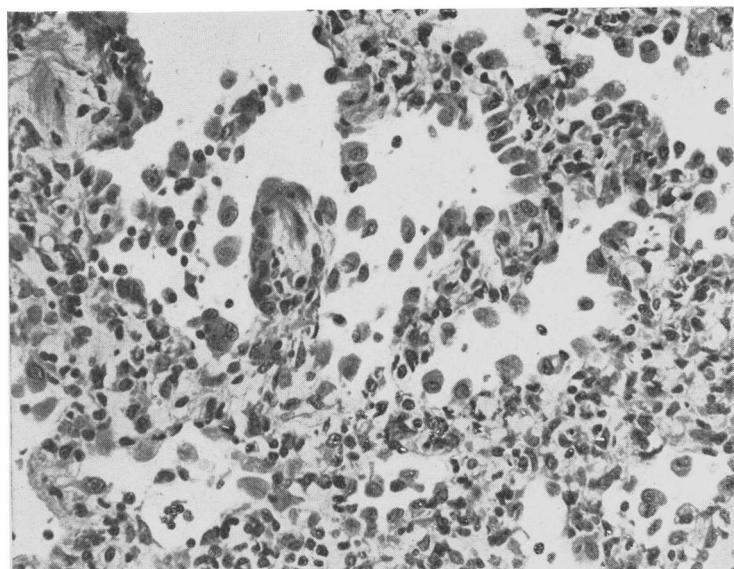


FIG. 1.—Histological appearance of patient's own left lung removed at operation. An increased number of large cells can be seen lining a respiratory bronchiole and its alveoli. Alveolar walls are thickened by an infiltrate of inflammatory cells. (H. and E. $\times 300$.)

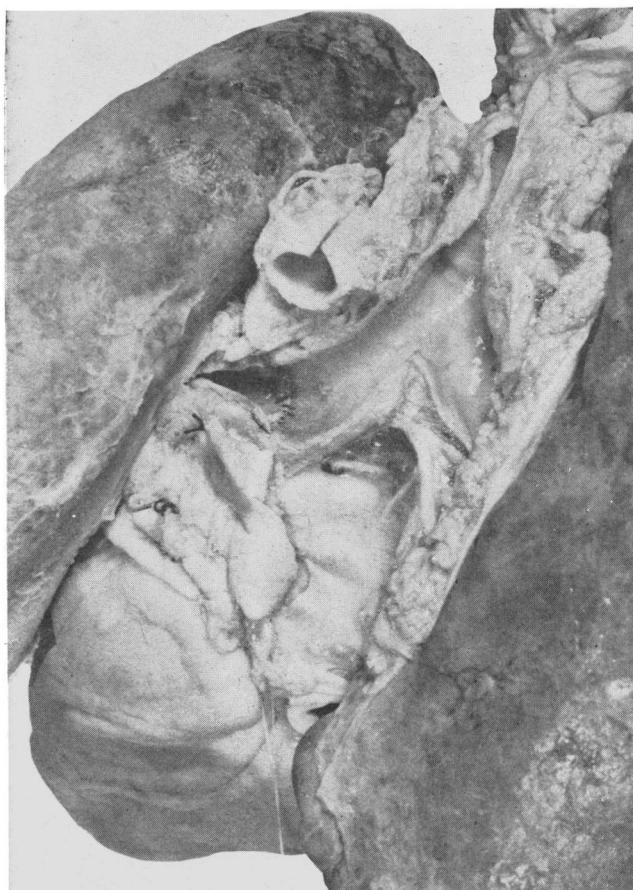


FIG. 2.—Posterior view of mediastinum showing transplanted lung on left of the photograph and bronchial anastomosis with sutures in place. Note fibrin on transplanted lung.

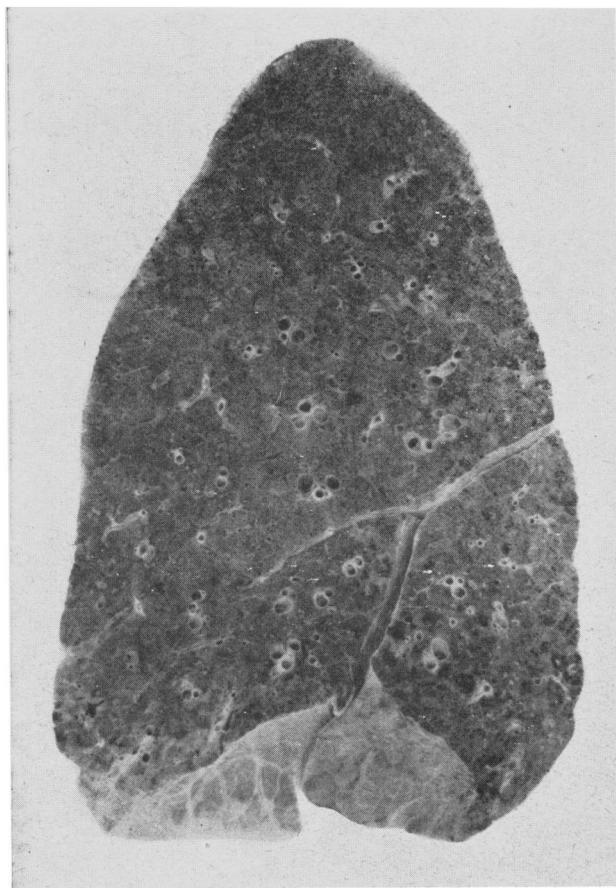


FIG. 3.—Slice of patient's own right lung removed at necropsy. There is fibrosis and fine emphysema in all areas, but it is most marked posteriorly and inferiorly. The small dark foci are haemorrhage. (Approximately one-half natural size.)

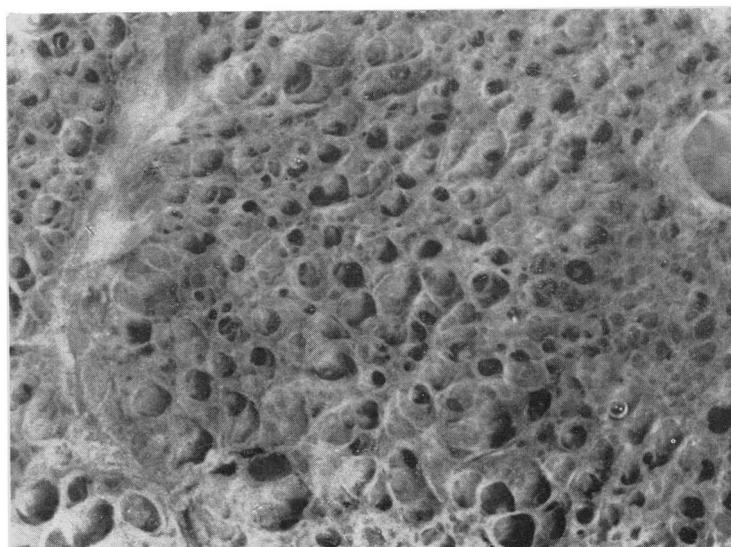


FIG. 4.—Higher magnification of slice of right lung seen in Fig. 3. Alveoli are absent from most areas and the surviving air-spaces appear to be fibrosed respiratory bronchioles and alveolar ducts. See also Fig. 5. ($\times 7$.)

HENRY MATTHEW ET AL.: PARAQUAT POISONING—LUNG TRANSPLANTATION

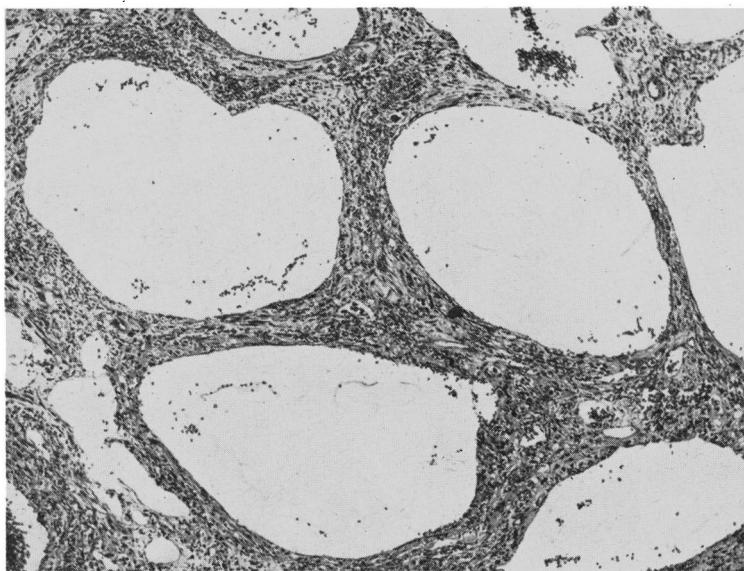


FIG. 5.—Histological appearances of right lung in an area such as that in Fig. 4. Alveolar walls have gone, and the walls of surviving respiratory bronchioles and alveolar ducts are thickened by proliferating fibroblasts (see Fig. 15). Many of the cells in the walls are red cells. (H. and E. $\times 70$.)

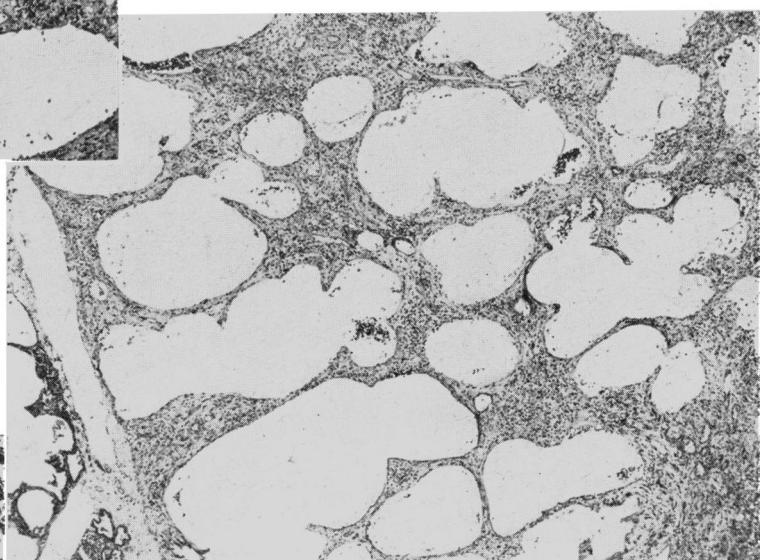


FIG. 6.—Histology of transplanted lung showing emphysema and fibrosis. Note similarity to Fig. 5 of patient's own right lung. (H. and E. $\times 30$.)

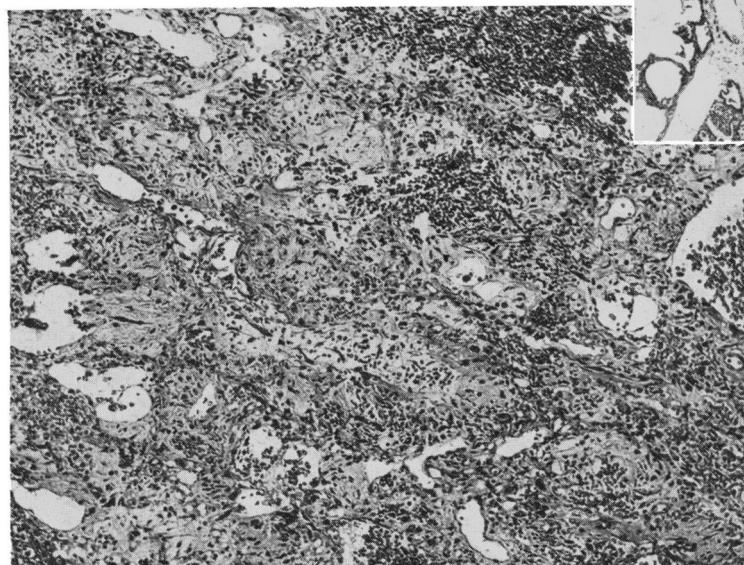


FIG. 7.—Section of right lung showing fibrous obliteration of air-spaces. Most of the dark dots are red cells. (H. and E. $\times 85$.)

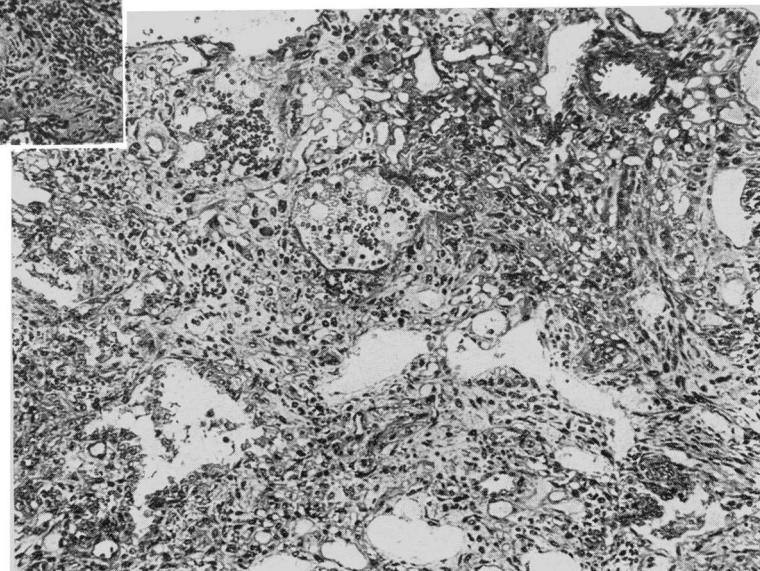


FIG. 8.—Histology of transplanted lung showing dense fibrosis by plump fibroblasts obliterating alveoli. There is a normal pulmonary arteriole in right upper quadrant. The appearance is similar to Fig. 7 of the patient's right lung. (H. and E. $\times 110$.)

HENRY MATTHEW ET AL.: PARAQUAT POISONING—LUNG TRANSPLANTATION

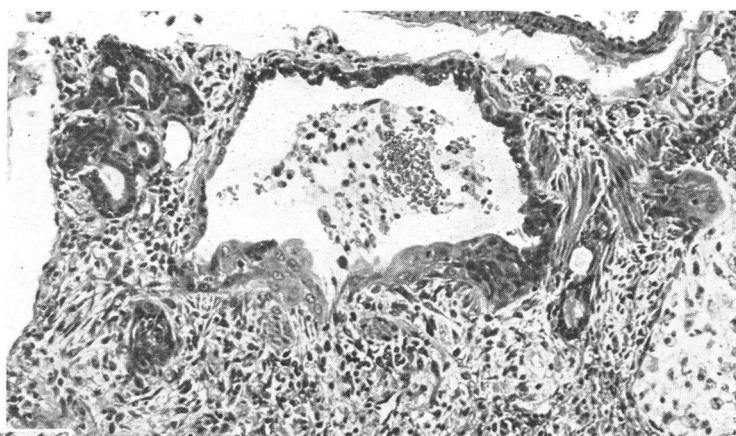


FIG. 9.—Section of right lung showing gland-like proliferation of bronchiolar epithelium. The walls show proliferating fibroblasts and chronic inflammatory cells. (H. and E. $\times 140$.)



FIG. 10.—Histology of transplanted lung showing gland-like proliferation of bronchiolar epithelium and also proliferating fibroblasts and chronic inflammatory cells. Red cells are numerous in the upper left quadrant. The appearance is similar to Fig. 9 of the right lung. (H. and E. $\times 140$.)



FIG. 11.—Higher magnification of the apical segment of a slice of transplanted lung showing normal alveoli in lobule on right of field and emphysema and pale fibrosis of lobule on left. ($\times 7$.)



FIG. 12.—Another view of the slice of transplanted lung. Emphysema and fibrosis is seen in upper lobe (on right of fissure) and denser fibrosis in the lower lobe (on left of fissure). ($\times 7$.)

HENRY MATTHEW ET AL.: PARAQUAT POISONING—LUNG TRANSPLANTATION

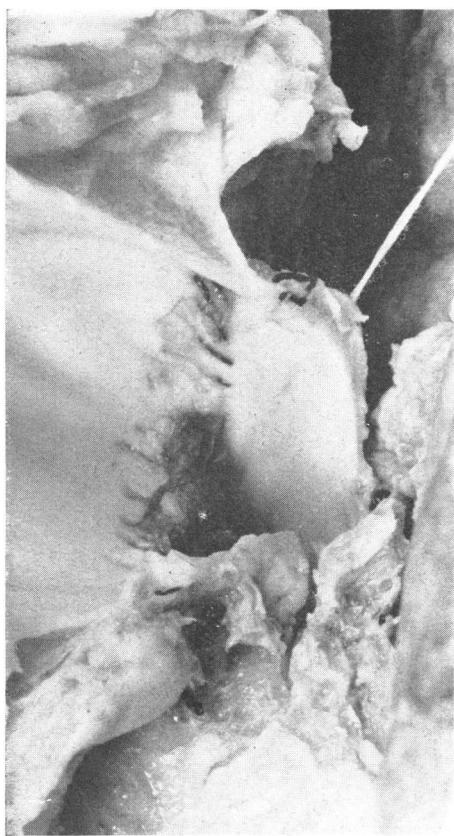


FIG. 13.—Anastomosis of pulmonary artery with transplanted artery on right of photograph. There is a small thrombus over part of the suture line.

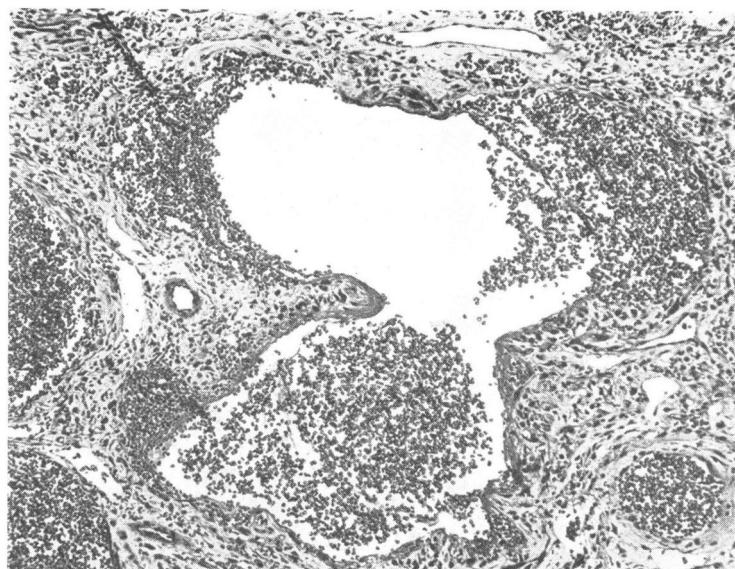


FIG. 14.—Histology of an area of haemorrhage in the right lung. The abnormally large air-spaces with fibrous walls contain red cells and fibrin. Part of the fibrin forms hyaline membranes lining the spaces in some parts. (H. and E. $\times 100$.)

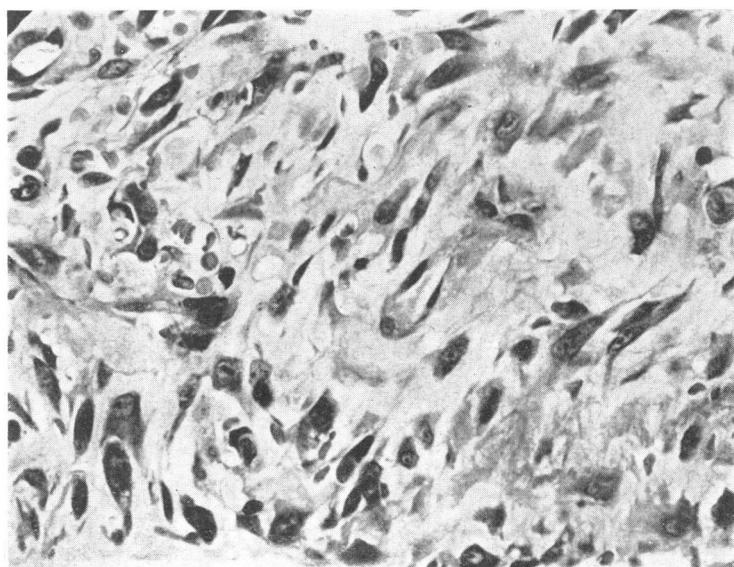


FIG. 15.—Section of right lung showing plump proliferating fibroblasts. (H. and E. $\times 450$.)

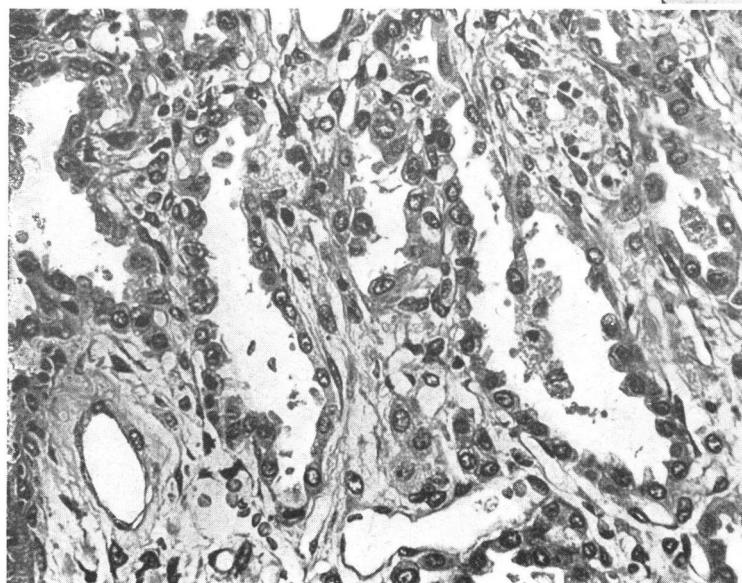


FIG. 16.—Histology of transplanted lung showing alveoli lined by large cells. (H. and E. $\times 350$.)

lung revealed radiographic changes now very similar to those on the right side.

Toxicological examination of the patient's own right lung after death showed no paraquat; the left lung, removed 13 days previously at operation, had contained 850 µg. of paraquat per 100 g. of wet lung tissue. The transplanted lung also contained no paraquat, but this does not exclude paraquat changes as the work of Clark *et al.* (1966) had shown.

One major feature of the pathological findings was the presence of histological changes in the patient's lungs which corresponded completely with those described in animals (Clark *et al.*, 1966) and in man (Bullivant, 1966; Almog and Tal, 1967; Oreopoulos *et al.*, 1968). These included haemorrhages, hyaline membranes, interstitial proliferation of plump fibroblasts in diffuse and whorled patterns, proliferation of bronchiolar and alveolar epithelium, and infiltration by chronic inflammatory cells. The changes are probably not wholly specific to paraquat, but are certainly different from the pattern of hexamethonium lung and busulphan lung, both of which show intra-alveolar rather than interstitial fibrosis (Heard and Cooke, 1968). The hyaline membranes appear to be the consequence of intra-alveolar haemorrhage rather than fibrinous oedema, though Manktelow (1967) has suggested that loss of surfactant may be important. The way in which alveolar walls are destroyed with the production of emphysema has not been studied by previous workers, and may subsequently throw light on the mechanisms involved in the production of emphysema and honeycomb lung.

The other main pathological feature was the presence of the same changes of paraquat in the transplanted lung. Figs. 5 and 6, 7 and 8, 9 and 10, and others may be matched to demonstrate the similarities in histological appearances of the right and transplanted lungs post mortem. The complex possibilities of other factors contributing to the changes in the transplanted lung cannot be ignored, especially the chance of a modified rejection phenomenon. Rejection of the lung in canine homologous transplantation without immunosuppression takes the form of massive haemorrhagic necrosis within one week to 10 days and a heavy infiltration of vessels and parenchyma by a variety of acute and chronic inflammatory cells from the recipient (Neptune *et al.*, 1953; Barnes *et al.*, 1963). With immunosuppression, the alveolar architecture has been found to be preserved and the cellular infiltrates prevented (Hardy *et al.*, 1963a, 1963b, 1964; Nakagawa *et al.*, 1967; Zajtchuk *et al.*, 1967). The major problems in dogs have been surgical, including necrosis of the bronchial stump through ligation of the bronchial arteries, and thrombosis of the vessels, especially at the anastomoses.

In the present patient there were no changes in vessels or parenchyma which could be attributed to rejection. The inflammation of the transplanted bronchi is considered to be due to the unavoidable loss of a bronchial artery supply, and the bronchial stump was left as short as possible at operation on this account. The left pneumothorax may have originated at the inflamed junction of the bronchial stump, but this could not be reproduced by inflation of the lungs post mortem.

Many colleagues contributed to the management of this patient. It would, however, be invidious to name the physicians, surgeons, nurses, and those in the professions supplementary to medicine to whom we owe thanks for their unstinted help. Imperial Chemical Industries provided useful information. We are also indebted to the procurator-fiscal for his enlightened approach to problems of organ transplantation.

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